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EXAMINER	
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ART UNIT	PAPER NUMBER
1641	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/905,293	Rosok et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1641

☒ Responsive to communication(s) filed on *Aug 12, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-52* is/~~are~~ pending in the application.

Of the above, claim(s) *23-27 and 32-52* is/~~are~~ withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22 and 28-31* is/~~are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-52* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Amendment

1) Acknowledgment is made of Applicants' amendment filed 06/14/99 (paper no. 10) in response to the non-final Office Action mailed 02/11/99 (paper no. 9). With this, Applicants have amended the specification.

Claims Status

2) Claims 3, 13, 14, 17, 18, 21 and 22 have been amended.

Claims 1-52 are pending.

Claims 1-22 and 28-31 are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' supplemental information disclosure statement filed 06/14/99 (paper no. 11). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 12).

The Examiner appreciates Mr. Joe Sorrentino's efforts in providing the Office with the publication number for the application 95/305,444, which is recited repeatedly in the instant application as an European application published March 6, 1996. See for example, pages 12, 21 and 27. The application has been published as EP 0 699 756 A1.

It has been noted that Exhibit 2, WO 94/29351, submitted by Applicants via PTO-1449 filed 02/02/98 is incomplete. Applicants have provided only the first 16 pages of the document. The complete document consists of a total of 91 pages. As a courtesy, the whole document has been obtained and placed in the case file.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection Withdrawn

6) The objection to the specification made in paragraph 8 of the Office Action mailed 02/11/99 (paper no. 9) is withdrawn in light of Applicants' amendment to the specification.

Objection Maintained

7) The objection to the drawings made in paragraph 6 of the Office Action mailed 02/11/99 (paper no. 9) is maintained for reasons set forth therein.

Rejections Withdrawn

8) The rejection of claims 2, 13, 14, 17, 18, 21 and 22 made in paragraph 9(a-c) of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C. § 112, second paragraph, is withdrawn in light of Applicants' amendment to the claims.

9) The rejection of claims 13, 14, 17, 18, 21 and 22 made in paragraph 13 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C § 112, first paragraph, with regard to the deposit issue, is withdrawn in light of Applicants' amendment to the claims and Applicants' compliance under 37 C.F.R. § 1.801-1.809.

10) The rejection of claims 21 and 22 made in paragraph 11 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C § 112, first paragraph, with regard to the recitation "derivative", is withdrawn in light of Applicants' amendment to the claims.

Applicants' Arguments & the Office's Response

11) Applicants contend that:

a) Morgan *et al.* teach methods which utilize antibodies having alterations in a single toxicity associated domain, but do not teach the use of antibodies having alterations in multiple toxicity associated domains for *in vivo* use. Applicants contend that the antibodies used in the instant invention (see page 6 of Applicants' amendment filed 06/14/99 - paper no. 10):

> ....have alterations both in a toxicity associated domain in the C-terminal region of the CH2 domain (roughly localized to amino acids 310-331) as well as alterations in a toxicity associated domain in the N-terminal region of the CH2 domain (roughly localized to amino acids 231-238)....

Applicants further state that Morgan *et al.* fail to provide any insight on which alterations in CH2 are associated with a reduction in immunoglobulin-induced toxicity (see page 8 of the Applicants' amendment filed 06/14/99 - paper no. 10).

Applicants' arguments have been considered, but are not persuasive. The instant claims, as drafted currently, do not include limitations of alterations in the immunoglobulin involving toxicity associated domain in the C-terminal and N-terminal regions of the CH2 domain. Claims generically recite "altering multiple toxicity associated domains in the constant region". See below under paragraph 12.

b) With regard to the reference of Gillies *et al.*, Applicants' contend that the mutants taught by Gillies *et al.* exhibit "little ADCC or CDC activity".

Contrary to Applicants' contention, Gillies *et al.* teach antibody mutants having "little ADCC or no (CDC) biological activity" (see line 7 of abstract).

c) Applicants contend that Yelton *et al.* disclose functional equivalents of mutant BR96 antibody "which do not include the Fc region do not exhibit ADCC or CDC properties" and Muroi *et al.* teach antibodies that bind to Lewis X antigen, but combination of these with Morgan *et al.* does not result in antibodies having alterations in multiple toxicity associated domains which can be used in methods of inhibiting immunoglobulin-induced toxicity (see page 9 of Applicants' response filed 06/14/99).

Applicants are reminded that the references of Gillies *et al.*, Yelton *et al.* and Muroi *et al.* are used in a **103** rejection to reject claims 3, 4, 6 and 11-22, not as anticipatory references in a 102 rejection. Yelton *et al.* is cited to document that the antibodies recited in the instant claims having specific ATCC accession numbers are known in the art, and so also their binding specificity to Lewis Y antigen and their therapeutic use as a fusion protein and as a component of an immunoconjugate. Most importantly, Yelton *et al.* teach functional equivalents of the mutant BR96 antibody that do not exhibit ADCC **or** CDC properties (see column 20, lines 51-53). Muroi *et al.* is cited to document that antibodies that bind to Lewis X antigen are also known in the art.

Applicants do not dispute that Gillies *et al.* teach antibody molecules having alterations in multiple toxicity associated domains, but argue that a combination of this with Morgan *et al.* in the manner suggested would not result in the instant invention. Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the

claimed methods are obvious over the prior-art methods, given the teachings of Morgan *et al.*, Gillies *et al.*, Yelton *et al.* or Muroi *et al.* The invention as a whole, would have been obvious to a practitioner in view of the contemporary knowledge in the art at the time of invention, the state of the art at the time of the invention (see below) and the combined teachings of the references applied. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

Rejections Maintained

12) The rejection of claims 1, 2, 5 and 7-10 made in paragraph 13 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C § 102(b) as being anticipated by Morgan *et al.* (WO 94/29351) is maintained for reasons set forth therein and those that are set forth below.

Morgan *et al.* disclose methods of treating diseases in which antibody or immunoglobulin therapy leads to undesirable toxicity or ADCC due to antibody mediated complement fixation comprising administering to a human or animal subject an altered or modified antibody (having a variable and a constant region), wherein one or more amino acid residues in the CH_2 domain of the antibody are altered such that the ability of the antibody to fix complement is altered (see pages 5 and 12). "The constant region of the antibodies to be altered according to the invention may be of animal origin and is preferably of human origin. It may also be of any isotype" (i.e. IgG, IgM or IgA), "but is preferably human IgG and most preferably human IgG1" (see page 6, first paragraph). These antibodies can be natural antibodies, chimeric antibodies, CDR-grafted antibodies or humanized antibodies (see page 13). The altered antibodies can be produced recombinantly (see page 13). The alteration in the constant region of the antibody can be produced by site directed mutagenesis (see page 14). The ability of the resultant antibody with altered constant region to fix complement or mediate ADCC, is "substantially reduced" (see page

6, fifth paragraph and page 7). Morgan *et al.* further teach an antibody "which fully retains its immunosuppressive properties but which has substantially reduced toxicity". The antibody is tolerated *in vivo* (see page 7). The alteration may comprise substitution, replacement, insertion or deletion of one or more amino acid residues (see page 9). For example, Morgan *et al.* teach an antibody molecule having alteration at 243 and being unable to mediate ADCC, and an IgG4 having the Leu235 to Glu alteration with abrogated ADCC. Changing the glycine at 237 to alanine of IgG1 also abolished FcR1 binding and reduced complement fixation and FcRIII mediated function. Alteration of the whole regions 233, 234, 235 and 236 (i.e., multiple regions) by exchanging with the sequence found in IgG2 abolished multiple functional properties such as FcR1 binding and complement fixation, and reduced FcRIII mediated function of IgG1 (pages 37 and 40). The alteration in the CH_2 domain of the antibody while altering the ability to fix complement can additionally inhibit the binding to FcR1 receptors (see page 8). Specific alterations at specific amino acid positions result in altered human antibodies with potent immunosuppressive ability with minimal toxicity (see page 9). Therapeutic and pharmaceutical uses of these altered immunoglobulins are taught in therapy and diagnosis of diseases (see pages 10 and 11). Examples of a variety of immunological diseases and conditions which can be treated with antibodies or immunoglobulins with altered constant region are disclosed including cancer immunotherapy (see page 12). For instance, the composition comprising the altered immunoglobulin is used in methods of therapy and diagnosis comprising "administering an effective amount" to a "human or animal subject" in therapeutic doses of 0.1-25 mg/kg body weight. The composition is used in the immunotherapy of many conditions including cancer and GI tract disease (see entire page 12) "without producing any significant adverse toxic effects", for example, those mediated via complement fixation (see page 1). Thus, a method of *in vivo* administration of an antibody structurally altered in multiple toxicity associated regions wherein the antibody exerts minimal or no toxicity is disclosed by Morgan *et al.*

Morgan *et al.* anticipate the instant invention.

13) The rejection of claims 3, 4, 6 and 11-22 made in paragraph 15 of the Office Action mailed 02/11/99 (paper no. 9) are rejected under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) as applied to claim 1 or 2 above, and in view of Yelton *et al.* (US

5,792,456) or Muroi *et al.* (*Blood* 79: 713-719, 1992, abstract) taken with Gillies *et al.* (*Human Antibodies and Hybridomas* 1: 47-54, 1990) is maintained for reasons set forth therein and those that are set forth below.

Instant invention encompasses methods for "inhibiting or **reducing** toxicity" to normal cells associated with immunoglobulin immunotherapy (see page 3, lines 18 and 19 of instant specification) using a structurally altered immunoglobulin, exhibiting "**reduced** or inhibited" toxicity (see paragraph bridging pages 3 and 4 of instant specification) (Emphasis added). The structural alteration is effected such that it results in "reducing or inhibiting" Ig-induced toxicity (see page 4, lines 4-5). On page 9 of the specification, Applicants define the term "inhibiting immunoglobulin induced toxicity" as meaning, "to **reduce** or alleviate" symptoms generally associated with toxicity (Emphasis added). The structurally altered molecule is stated to exhibit "a diminished ability to induce toxicity" (see page 10) as opposed to total loss of ability to induce toxicity. The specification further recites that "the methods of the invention encompasses the use of structurally altered immunoglobulin molecules regardless of whether it mediates a CDC or ADCC response" (see page 10). It is further recited that "the underlying requirement for any structural alteration of the constant region is that immunoglobulin-induced toxicity is substantially reduced or inhibited" (Emphasis added). The altered antibody molecule encompassed in the instant invention can be one whose "ability to mediate a CDC response **or** ADCC response and/**or** activate the complement cascade is prevented or inhibited" (see page 15) (Emphasis added). The instant invention, as recited in the paragraph bridging pages 14 and 15, encompasses a structurally altered immunoglobulin wherein only the CH2 domain is deleted which results in a "molecule unable to bind to the Fc receptor **or** a complement component". In another embodiment, only that portion of the CH2 domain which binds the complement C1q is deleted" (see page 15).

The teachings of Morgan *et al.* are described above, which do not disclose the use, in their method, of an Ig fusion protein, BR96 or ChiBR96 with altered structural constant region as recited in instant claims and with an ability to bind to Le^y or Le^x.

Yelton *et al.* disclose a monoclonal antibody BR96 produced by the hybridoma HB10036, and a ChiBR96 produced by the hybridoma HB10460, both deposited at the ATCC (see column 1

and 2). Note that the antibodies recited in instant claims 13, 14, 17, 18, 21 and 22 have the same ATCC accession numbers. A mutant BR96 is also taught (see column 7). It is disclosed that BR96 recognizes and binds Le^y or Lewis Y antigen (see column 1). A fusion protein of the mutant BR96 which can be used to treat human carcinoma is taught (see column 10). It is disclosed that BR96 can be used as a fusion protein, or as a mutant IgG, or mutant Fab, or mutant $F(ab')_2$, or as an immunoconjugate after conjugating it to a cytotoxic agent such as doxorubicin or a therapeutic agent such as *Pseudomonas* exotoxin A (see column 11). Preclinical studies done with such a conjugate are discussed (see column 2). Yelton *et al.* teach BR96 or mutant BR96 conjugated to a cytotoxic agent selected from the group consisting of antimetabolites, ankylating agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents (see claims 29 and 30). It is taught that "because of the toxin or drug, the conjugate is more potent than non-conjugated mutant BR96" (see column 12). Explicitly taught are functional equivalents of mutant BR96 antibody that do **not** exhibit ADCC or CDC properties (see column 20, lines 51-53). The antibody can be administered *in vivo* and can be conjugated or linked to a therapeutic drug or toxin for delivering the therapeutic agent to the site of the carcinoma (see column 20). It is taught that introduction of mutations to BR96 did not adversely affect tumor specificity nor significantly increase binding to normal tissues (see column 35). Thus, the BR96 antibody with multiple mutations (see Example 6) and that does not exhibit ADCC or CDC properties is taught.

C term of CH2 310-331

N term. CH2 231-238

Muroi *et al.* teach monoclonal antibodies that recognize and bind to Le^x (see abstract).

Gillies *et al.* teach that their approach was to delete the CH2 domain of the molecule in such a way that it removes multiple properties involving changes in multiple sequences, i.e., the sequence responsible for "binding of the Fc receptor on effector cells", the sequence to which the single N-linked carbohydrate chain is attached, and the sequence to which the first complement component, C1q, binds" (see pages 52 and 53). The ΔCH2 mutant disclosed by Gillies *et al.* does not mediate complement lysis because it lacks the sequence to which C1q binds. The mutant antibody also shows loss of ability to mediate ADCC, thus reflecting the loss of the sequence responsible for binding the Fc receptors. Note that the site for binding of the FcRI has been mapped to the CH2 domain (see page 53) and the biological activity of the CH2 domain is greatly affected by the presence of the single N-linked carbohydrate moiety in the middle of the CH2

Morgan teaches this to be at 318, 320, 322 - conserved in human IgG1, rat, mouse, e.g. Pig & rabbit

domain (see page 54). It is clearly taught that certain alterations in the CH2 domain affect **both** complement and Fc receptor binding (see page 54). Thus, a CH_2 mutant with no ability to mediate complement lysis and a Cγ1S mutant with less efficient ability to mediate complement mediated lysis are taught (see pages 52-54). The structurally altered antibodies having greatly reduced ADCC activity are useful for labeling and imaging of tumors (see page 54) where the loss of effector function or Fc receptor binding is desired (see abstract).

It would have been obvious to one skilled in the art at the time the invention was made to modify Yelton's BR96 or ChiBR96 or fusion protein having known tumor-specific activity and ability to bind Le^y antigen, or Muroi's antibody with an ability to bind Le^x antigen, using Gillies' or Morgan's structural alterations affecting multiple toxicity-associated areas in the constant region, and use the resulting altered immunoglobulin or fusion protein in Morgan's method of treating or inhibiting immunoglobulin-induced toxicity in an animal or a human subject to produce the instant invention with a reasonable expectation of success. One skilled in the art would be motivated to produce the instant invention because: 1) BR96 or ChiBR96 are well characterized therapeutic molecules whose *in vivo* tumor specificity and ability to bind Le^y antigen have been established in the art as taught by Yelton *et al.*; 2) There is an identified need in the art to have therapeutic or prophylactic antibody or immunoglobulin agents that do not mediate ADCC or activate complement during immunoglobulin immunotherapy as taught by Morgan *et al.*, and 3) It is known in the art that functional equivalents that do **not** exhibit ADCC or CDC properties can be derived from the mutant BR96 antibody as explicitly taught by Yelton *et al.* A skilled artisan would choose an immunoglobulin such as the one disclosed by Yelton *et al.* i.e., the mutant BR96 or ChiBR96 mutant or the fusion protein, for altering the constant region because BR96 mutants are well characterized and well studied *in vivo* including in a conjugate form and are known to have intact tumor specificity as taught by Yelton *et al.*

Claims 3, 4, 6 and 11-22 are obvious over the cited prior art.

14) The rejection of claims 28-31 made in paragraph 16 of the Office Action mailed 02/11/99 (paper no. 9) under 35 U.S.C. § 103(a) as being unpatentable over Morgan *et al.* (WO 94/29351) as applied to claims 1 or 5 above, and further in view of Yelton *et al.* (US 5,792,456) is

maintained for reasons set forth therein and those that are set forth below.

The teachings of Morgan *et al.* are explained above which do not disclose conjugating the altered antibody or immunoglobulin or fusion protein to a cytotoxic agent.

The teachings of Yelton *et al.* have also been explained above.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to conjugate Morgan's antibody having the altered constant region, or Yelton's fusion protein as modified by Morgan's alterations to Yelton's cytotoxic agent selected from the group consisting of antimetabolites, ankylating agents, anthracyclines, antibiotics, anti-mitotic agents and chemotherapeutic agents to produce the method of the instant invention, with a reasonable expectation of success, because Yelton *et al.* teach that it is conventional to conjugate an antibody or immunoglobulin or fusion protein to a cytotoxic agent for the purpose of delivering the therapeutic agent to the target site, for example, the site of carcinoma. One skilled in the art would be motivated to conjugate Morgan's altered antibody or Yelton's fusion protein as modified by Morgan *et al.* to one of Yelton's cytotoxic agents for the expected benefit of obtaining a therapeutic immunoconjugate having no antibody dependent cellular cytotoxicity, but which would be more potent than the non-conjugate mutant antibody as taught by Yelton *et al.*

Claims 28-31 are obvious over the prior art of record.

Relevant Prior Art

15) The prior art made of record and not relied upon currently in any of the rejections is considered pertinent to Applicants' disclosure:

- Dorai *et al.* (*Hybridoma* 10: 211-217, 1991, abstract) teach a chimeric IgG antibody with the N-linked carbohydrate attachment site eliminated. The antibody does not exhibit any ADCC activity.
- Lo *et al.* (*Human Antibodies Hybridoma* 3: 123-138, 1992, abstract) teach a CH2-deleted chimeric antibody shown to be useful for radioimmunodetection of human tumors.
- Chiorini *et al.* (*Int. J. Cancer* 53: 97-103, 1993, abstract) teach a CH2 domain-deleted recombinant immunoglobulin for clinical use.

Calvo *et al.* (*Cancer Biother.* 8: 95-109, 1993, abstract) teach the construction and purification of domain-deleted immunoglobulin variants of a recombinant monoclonal

antibody. The antibody lacks the sequences that encode the CH2 domain, CH3 domain, or **both**, and still maintains antigenic specificity.

- Chiorini *et al.* (*Cancer Res.* 55: 5957s-5967s, 1995, abstract) teach biological properties of chimeric domain-deleted anticarcinoma immunoglobulins.
- Robinson *et al.* (*Human Antibodies Hybridoma* 2: 84-93, 1991, abstract) teach chimeric anti-carcinoma antibodies having undetectable or very weak ADCC activity. One of the antibodies does not also mediate CDC of breast carcinoma cell lines.
- Mueller *et al.* (*PNAS* 87: 5702-5705, 1990 - Applicants' IDS) teach a chimeric antibody deleted of the CH2 domains.

Remarks

16) Claims 1-22 and 28-31 stand rejected.

17) **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18) Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi whose telephone number is (703) 308-9347. The Examiner can

normally be reached on Monday to Friday from 8.00 a.m. to 4.00 p.m. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

August 1999

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641